A CELLULAR BASED MODEL OF THE MYOGENIC RESPONSE IN ISOLATED RAT CEREBRAL ARTERIES

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Abstract— **This study is concerned with the development of an integrated multiple compartment model of the isolated cerebral artery in rat. The smooth muscle/arterial wall complex is an important component of the circulatory model and serves as an "vasomotor organ", which provides the myogenic mechanism. We have focused on this myogenic mechanism and have developed a model of the electrophysiological, contractile and mechanical characteristics of the single smooth muscle cell. This cell model is used to interrelate the topics of arterial wall stress, changes in transmembrane potential, intracellular $[Ca^{2+}]_i$ concentration and smooth muscle contraction. Moreover, the small cell model is embedded in a larger arterial wall model, which converts contractile activity into changes in lumen diameter. The complete model is used to provide biophysically based explanations of the myogenic mechanisms underlying the autoregulation of cerebral blood flow.**

Keywords— **Myogenic Response, Smooth Muscle.**

I. Introduction

A luminal pressure increase in cerebral arterioles and small arteries produces an initial passive distension followed by a sustained constriction due to active force development in vascular smooth muscle cells. This process is termed the myogenic response and it plays a critical role in maintaining constant blood flow and pressure for microcirculation.

Several models have been developed to investigate various aspects of vascular smooth muscle function including Ca^{2+} dynamics, contractile kinetics and force generation [1], [2], [3]. Models have also been developed for isolated cerebral arteries [4], [5]. These topics are usually studied individually. An overall modeling approach, which integrates most functional compartments in different physiological levels including membrane electrophysiology of smooth muscle cell, smooth muscle contractile mechanism and arterial mechanical properties, is needed to give a complete picture and better understanding of this physiological system behavior with regard to myogenic response.

In the current study, we developed a mathematical model to describe the electrophysiological, biochemical and mechanical processes of single vascular smooth muscle cell, and hence the cellular aspects involved in the mechanism of myogenic response. The single cell model is considered as a basic functional unit, and is subsequently coupled to a mechanical model of arterial vessel which describes the elastance and pressure-volume relationship of the isolated cerebral artery. This integrated model serves as a general framework that can be used to examine physiological hypotheses, and also provide mechanistically based explanations of experimental phenomena.

II. Model Development

A. Model of Single Smooth Muscle Cell

A.1 Model of Cell Electrophysiology

Fig. 1 shows the diagram of the model for smooth muscle cell electrophsyiology.

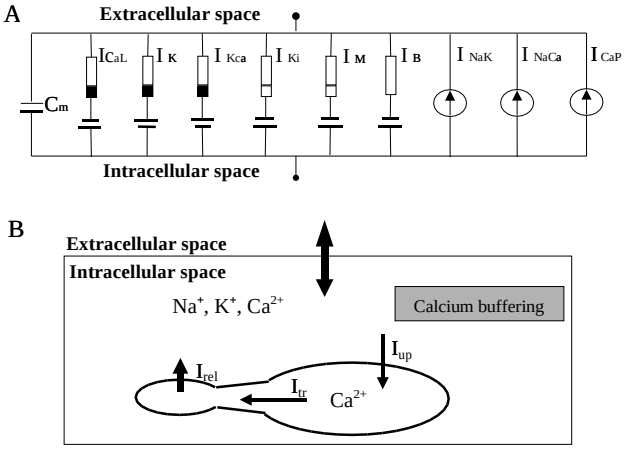

Fig. 1. **Cell Electrophysiological model** . A. The model describing membrane currents and transmembrane potential. B. The fluid compartment describing ionic dynamics and Ca^{2+} buffering, including Ca^{2+} handling by sarcoplasmic reticulum (SR).

Fig.1A represents a Hodgkin-Huxley type electrical equivalent circuit of the smooth cell membrane, which consists of a whole-cell membrane capacitance (C_m) shunted by a variety of resistive transmembrane channels including the L-type Ca^{2+} channel ($I_{Ca,L}$), mechanically sensitive channel (I_M), Ca^{2+} activated K^+ channel ($I_{K,Ca}$), as well as, the inward rectifier(I_{Ki}), delayed rectifier (I_K) and background (I_B) currents. Na^+/K^+ and Ca^{2+} pump currents (I_{NaK} and I_{CaP})and the Na^+/Ca^{2+} exchanger current (I_{NaCa}) are also included. Kirchhoff's current law applied to the equivalent circuit of Fig.1A yields the following differential equation describing changes in transmembrane potential V_m:

$$\frac{dV_m}{dt} = -\frac{1}{C_m}(I_{Ca,L}+I_K+I_{K,Ca}+I_{Ki}+I_M+I_{NaCa}+I_{NaK}+I_{CaP}+I_B) \quad (1)$$

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Abstract

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To account for changes in the ionic concentrations of Na^+, K^+ and Ca^{2+} with voltage and time, a fluid compartment model (see Fig.1B)is developed, that is based on cytosolic ion balances for Na^+, Ca^{2+} and K^+. Concentrations for these ions are assumed to be constant in the larger extracellular bathing medium. The material balance for Ca^{2+} accounts for membrane Ca^{2+} influx from L-type Ca^{2+} channel (major pathway of Ca^{2+} entry), buffering by the cytosolic protein calmodulin (CM), and other buffering media, as well as, a secondary ryanodine sensitive Ca^{2+} induced Ca^{2+} release (CICR) mechanism of sarcoplasmic reticulum (SR) and Ca^{2+} extrusion via sarcolemmal and SR membrane Ca^{2+} pumps.

This model is based on various experimental studies reported in the literature and is able to predict responses to a variety of biophysical processes, most importantly the regulation of $[Ca^{2+}]_i$.

A.2 Ca^{2+}-CM Dependent Contractile Kinetics

The interaction between actin thin filaments and myosin thick filaments provides the molecular basis for muscle contraction which is regulated by intracellular calcium-calmodulin complex ($CaCM$). This complex binds to and activates the enzyme myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of myosin light chain, which results in an increase in actin-activated ATPase activity of myosin and initiates cross-bridge cycling and force generation [6], [7], [8].

We employ the four-state kinetic model developed by Hai and Murphy[2], [9] to describe myosin phosphorylation and latch bridge formation. Fig. 2 shows this model, which consists of four fractional species: free cross-bridges (M), phosphorylated cross-bridges (Mp), attached phosphorylated cross-bridges (AMp) and attached dephosphorylated cross-bridges *i.e.,* latch bridges (AM). The latch state has been found to be unique to smooth muscle, and it endows the smooth muscle cell with the ability to maintain force when the level of calcium-dependent myosin phosphorylation is relatively weak.

The population of phosphorylated myosin is defined as the sum $Mp + AMp$, whereas attached cross–bridges are represented by the sum $AMp + AM$. The $CaCM$ dependence of myosin phosphorylation is represented through rate constants K_1 and K_6. We assume $K_1 = K_6$ which means that the phosphorylation process has same rate in changing from M to Mp, as from AM to AMp. Thus,

$$K_1 = K_6 = f(CaCM) \tag{2}$$

A.3 Smooth Muscle Cell Mechanics

To study the active mechanical response and viscoelasticity of the single smooth muscle cell, a model of cell mechanics is developed to represent the coupling between the active force generation of myosin kinetics and the mechanical property of the myofilaments and the cell (Fig.3).

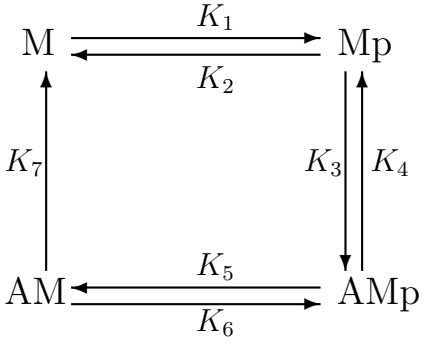

Fig. 2. **Multi–state kinetic model of calcium dependent myosin phosphorylation and cross–bridge formation**

The elastic response originating within the myofilaments of the cell is attributed to cross-bridge stiffness k_x in series with an series elastic element k_s having an exponential length-force (L:F) relationship [10], [11]. The passive elasticity of the cell is modeled as a parallel element k_p, which is characterized by nonlinear exponential (L:F) relationship.

The characteristics of the cross-bridges is described according to the force:

$$F_x = (k_{x1} \cdot AMp + k_{x2} \cdot AM) \cdot l_x \cdot e^{-\beta\left(\frac{l_a - l_{opt}}{l_{opt}}\right)^2} \tag{3}$$

where l_x is the extension of cross–bridge and l_{opt} is the optimal length of the overlap between myosin filament and actin. Both latch bridges and phosphorylated attached cross bridges contribute to the elasticity of this component. The spring constants k_{x1} and k_{x2} in equation (3) denote the maximal stiffness which can be achieved by latch bridges and phosphorylated attached cross–bridges, respectively. AMp and AM are considered as the outputs of the kinetic contractile model described in previous section, and indicate the distribution of attached cross–bridges and the state of interaction between myosin and actin filaments.

A model of active force generation is developed, based on the cross-bridge kinetics and the interaction between

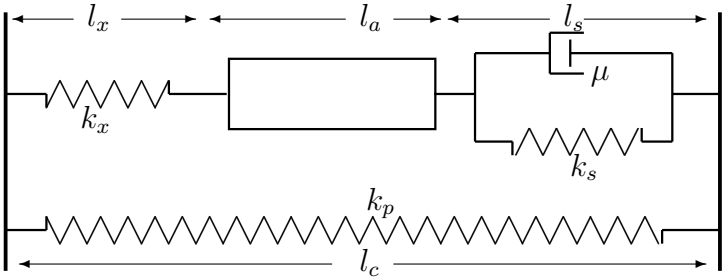

Fig. 3. **Mechanical model for smooth muscle cell** The two branches of the network represent the mechanical properties of the smooth muscle cell: k_p denotes the component for passive parallel elasticity, whereas k_x and k_s denote the elasticity of attached cross bridge and series elastic component, respectively. The active contractile (length l_a) element expresses the interaction between cross-bridges and actin filaments by cross-bridge cycling and sliding.

the cross–bridges and actin filament. The force developed by this element is described as:

$$F_a = [f_{AMp} \cdot AMp \cdot (v_x + \dot{l}_a) + f_{AM} \cdot AM \cdot \dot{l}_a] \cdot e^{-\beta\left(\frac{l_a - l_{opt}}{l_{opt}}\right)^2} \quad (4)$$

where f_{AMp} and f_{AM} are friction constants for latch bridges and phosphorylated cross bridges, respectively. The assumptions used by this formula are: (a) only attached phosphorylated cross bridges have cycling behavior moving actin filament with a linear velocity v_x. Note that this is the only process which contributes to the active force generation. The latch bridges lose cycling capability and remain attached to actin filament changing the stiffness of the cell (described in equation (3)); and (b) both species of attached cross bridges, phosphorylated and latch bridges, can move along the actin filament with a velocity $\dot{l}_a$ in response to cell stretch and release.

B. Vascular Wall Model

We also consider a macroscopic lumped model of the isolated perfused cerebral artery, in terms of its elastic properties and the properties of the perfusion system to which the vessel is attached via cannulation. The dynamic response of the whole vessel to a pressure pulse, causes changes in vessel diameter that are mediated by the stretch-activated response of individual smooth muscle cells. We define a lumped elastance function $E(t)$ for the vessel that characterizes the pressure -volume relationship for this distensible vessel. The smooth muscle cell model is incorporated into this larger vessel model and provides the dynamic changes involved in the change in vessel elastance with time. Specifically, we develop a vascular wall model based on a circumferential distribution of smooth muscle cells within the arterial wall. This is formulated as a model of vessel elastance $E(t)$, the instantaneous pressure-volume relationship of the isolated vessel, which is modulated by the activity of smooth muscle in the wall. Vessel stiffness and the hydraulic resistance R_i offered to blood flow are altered with changes in vessel elastance $E(t)$. This leads to the myogenic control of blood flow in cerebral vessel. The model diagram is shown in Fig.4

III. Model Simulations and Capabilities

This integrated model is used to simulate various experimental studies on both the single isolated smooth muscle cell and the isolated arterial vessel. When applied to study the myogenic mechanism of cerebral artery, the model is capable of mimicking the experimental work of Knot et al.[12]. Specifically the:

1. Steady-state relationship between intravascular pressure and membrane potential;
2. Steady-state relationship between intravascular pressure and arterial wall Ca^{2+} concentration;
3. Steady-state relationship between intravascular pressure and arterial wall Ca^{2+} diameter;

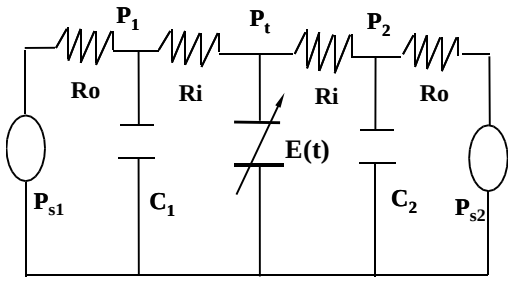

Fig. 4. **Diagram for the vascular model of isolated cerebral vessel and testing apparatus.**

4. Membrane potential manipulation by $[K^+]_o$ in the pressurized cerebral artery;
5. Ca^{2+} dynamics and active constriction of cerebral arteries in response to an elevated intravascular pressure.

IV. Summary

This integrated model provides insights summary into the cellular mechanisms involved in the myogenic autoregulation of cerebral blood flow.

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